MERCK

Making Biologics:

Strategies and Policies for Enhancing Capacity

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1. Introduction

The COVID-19 pandemic has shown that the cost of underinvesting in resilient systems for the development, production, and distribution of health technologies is too high. In particular, during the pandemic, it became abundantly clear that global supply chains for biologics – a category of products that includes vaccines, monoclonal antibodies (mAbs), recombinant proteins, plasma-derived proteins, and cell and gene therapies – can become dangerously strained during public health crisis.

Before this pandemic, the biologics market was growing quickly. This meant steadily rising demand for inputs and equipment to develop and manufacture these products. The urgent need to rapidly produce billions of COVID-19 diagnostic tests, vaccines, and treatments led to a sudden surge in demand for these inputs and equipment, causing shortages of critical manufacturing raw materials. The world witnessed the inability of global supply chains to cope with such a rapid, sudden, and significant increase in demand, as the shortcomings of the world's insufficient and centralized bio-manufacturing capacity were exacerbated.

The global community recognizes now that investments to improve the resilience of these supply chains, and to expand global production capacity for biologics, will be needed to ensure future pandemic preparedness and enhance healthcare delivery overall. Despite recent technological advances, manufacturing biologics remains challenging, particularly for countries that are still developing the necessary technical and financial capacity. Building blocks do exist, however, as do enormous opportunities. And encouraging progress has taken place rapidly in recent years, particularly since the outbreak of the pandemic.

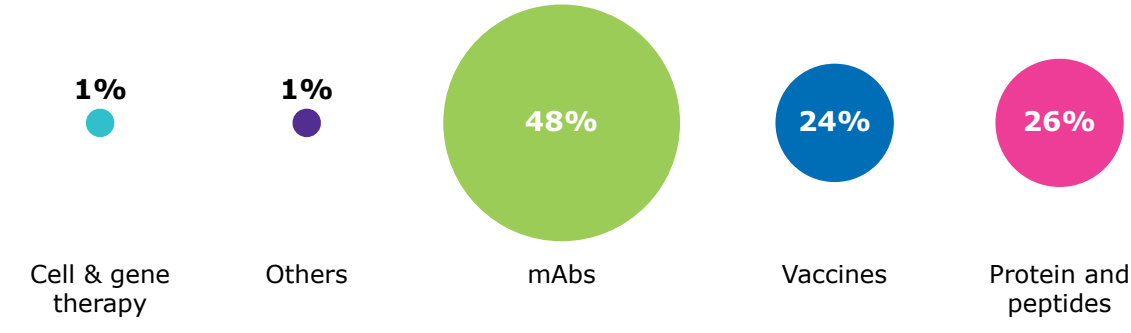
This paper introduces biologics, describes opportunities in the sector, and provides insights about the processes for manufacturing them. It then identifies the diverse pathways that countries have used in recent years to develop bio-manufacturing capacity. Finally, it looks to the future to identify the government policies and technology solutions that will enable more countries to join global value chains and to produce these life-saving treatments more safely, quickly, and cost-effectively – to the benefit of patients everywhere.

2. Opportunities in the Biologics Sector

Biologics are large molecules produced in living organisms or extracted from biological materials; they are different from small molecules, which are chemically synthesized. These complex products, which have a high therapeutic value, are manufactured by biotechnology companies and institutes.

The global human biopharmaceutical, or "biologics", market accounted for almost $270 billion in 2021 and is projected to continue to grow at high single digit rates. Growth in this market has been driven by several factors, including an increase in chronic diseases, such as cancer, in aging populations of industrialized countries, a growing prevalence of infectious diseases, and more adoption of and access to biologics worldwide.

Figure 1. BIOLOGICS TYPES AND THEIR CONTRIBUTION TO THE GLOBAL MARKET



Based on 2021 sales revenue
Source: Evaluate Pharma, March 2022

The global human biopharmaceutical, or "biologics", market accounted for almost $270 billion in 2021 and is projected to continue to grow at high single digit rates.

Biologics generally have a higher net present value (NPV) and are priced higher than small molecules. In the last 20 years, the return on biologics portfolio investments has increased, driven by reduced development times and increased probability of success. This has encouraged more investors and start-ups to focus on this industry.

Biopharmaceuticals encompass different product classes, used for different indications. These differ in their manufacturing processes and value.

While vaccines have gotten the lion's share of attention since early 2020 due to COVID-19, it is monoclonal antibodies, or mAbs, that are the leading product class among biologics. Their share of global revenue in the biopharma industry grew by more than 500% between 2007 and 2018. "Biosimilars" are biologicals that are produced similarly to original molecules and are nearly identical in terms of how they act in the body. These can be monoclonal antibodies, vaccines, or other biologics products like recombinant proteins.

The appetite for biologics – and especially for biosimilars – continues to grow worldwide. This is due to their cost-effectiveness, the rising incidence of chronic diseases, and improving healthcare infrastructure in many countries. While estimates vary, their prices can be 20% to 30% cheaper than the originator products. Biosimilars can therefore offer increased opportunity for patients, healthcare providers, and manufacturing companies alike.

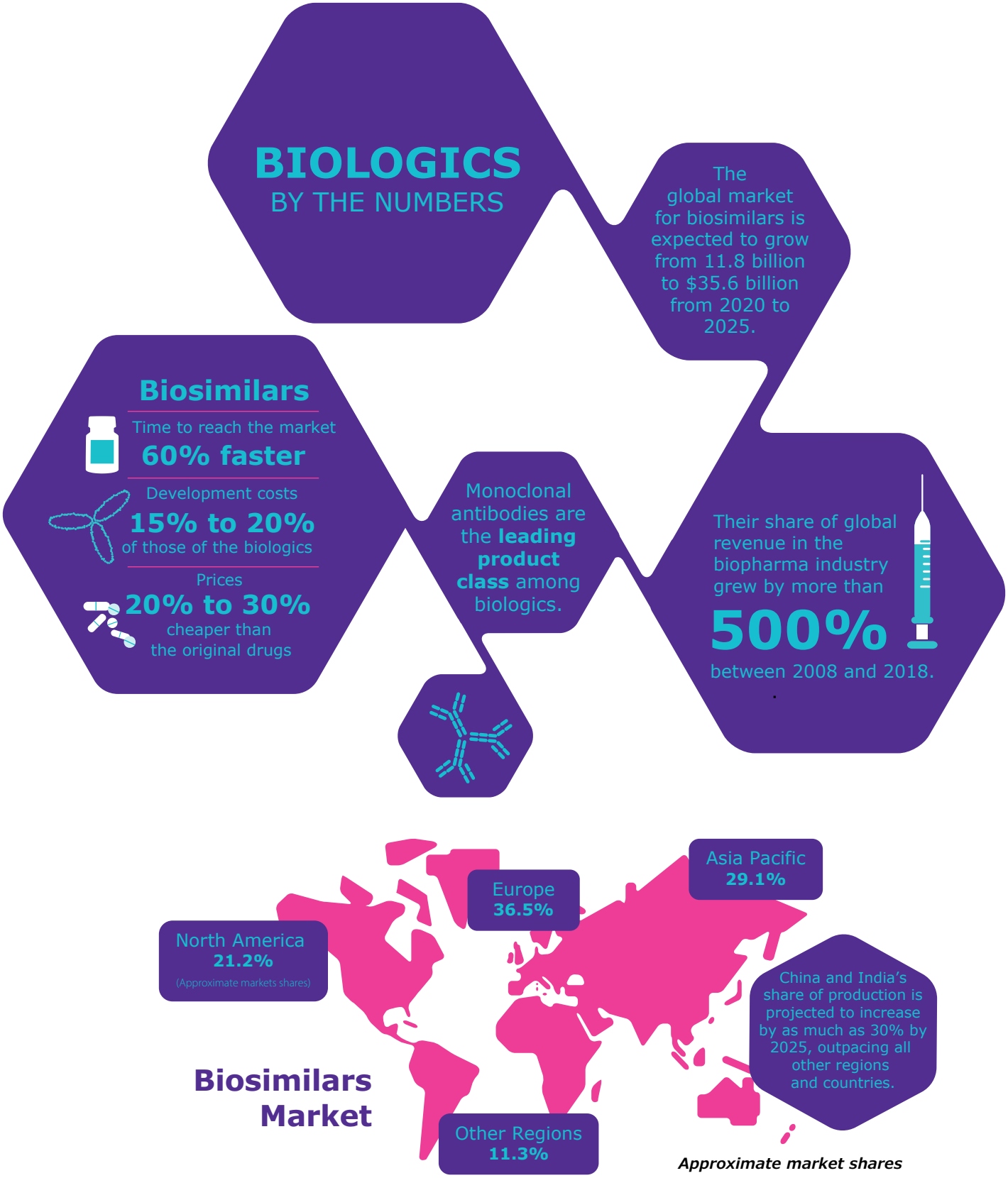
The global market for biosimilars is expected to grow from $11.8 billion to 35.6 billion from 2020 to 2025. In 2019, North America accounted for approximately 21.2% of the biosimilars market, with Europe at 36.5%, Asia at 29.1%, and other regions at around 11.3%. New opportunities in emerging markets, along with patent expiry on the originator products, are factors contributing to such growth in the biologics market in the coming years.

In terms of the production of biosimilars, while Europe currently holds most of the market share, low- and middle-income countries (LMICs) are rapidly increasing their capacity. China and India's share of production is projected to increase by as much as 30% by 2025, outpacing all other regions and countries.

Vaccines are arguably the best-known biologic product. By mimicking a disease, a vaccine prompts the body to produce antibodies that fight the invading pathogen. Because vaccines are so critical, public health policies, rather than market forces, have largely determined how they are manufactured, distributed, and priced in recent decades. In much of the developing world, they are primarily bought and distributed by the public sector. For example, the government is the largest purchaser of vaccines in South Africa, where vaccines that are part of the World Health Organization's Expanded Program on Immunization (EPI) are provided free of charge to 90% of the target population. Countries that are beneficiaries of the Global Alliance for Vaccination Initiative (GAVI), meanwhile, can receive vaccines for children courtesy of UNICEF, which purchases the supply at prices that are close to the cost of production.

This situation is changing. The list of countries slated to graduate from the GAVI program is increasing, creating a pool of prospective buyers for emerging vaccine manufacturers. Meanwhile, the shifting focus of advanced biotech manufacturers away from developing-country vaccines will open up opportunities for local producers. And following the COVID-19 pandemic, the call to "go local" has grown louder, leading governments to invest more in home-grown or regional manufacturing.

Figure 2. MONOCLONAL ANTIBODIES & BIOSIMILARS SPOTLIGHT



Sources: 17th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production; Biosimilars: Global Markets; and Biosimilars Market Global Forecast to 2023 and 2025[1]

Boosting local vaccine manufacturing can also make economic sense. Manufacturing in more places increases reliability and resilience of supply and reduces costs of transportation. Moreover, the acquisition of skills required for biologics manufacturing can reverberate across other sectors to stimulate development in additional industries. With better insight into the needs of their communities, particularly those related to tropical diseases, local producers are also better placed to serve patient needs in their countries.

The opportunities in the bio-manufacturing sector are not limited to China and India. In fact, manufacturers in all growing markets can now enter and move up biologics value chains more readily than in the past. This is partly thanks to recent technological innovations that have improved and simplified bio-manufacturing, while reducing the cost and time required to set up new facilities.

3. Biologics Manufacturing Strategies

Local production is one approach that can bring monoclonal antibodies within reach of more patients. Many LMICs already import monoclonal antibodies, and physicians and patients are thus already familiar with using them. Furthermore, several developing countries are already experienced in producing vaccines. This means that entering monoclonal antibodies production can be a logical next step.

Manufacturers of biologicals and, in particular, of monoclonal antibodies, must navigate a complex market, as well as a painstaking production process. Due to their complexity and the high concentration of final drug substance needed for a typical dose, the manufacturing cost-per-dose of monoclonal antibodies can be multiple orders of magnitude higher than that of vaccines. Moreover, vaccines are produced on a much larger, population-wide scale, allowing for economics of scale that are generally not available for monoclonal antibodies production; monoclonal antibodies are often targeted at diseases for which treatment options are limited. Biologics for cancer and autoimmune diseases are top-selling medicines, despite their price tag which can be as much as tens of thousands per patient per year. The market entry of biosimilars can bring the price down significantly, while patients benefit from a nearly identical treatment.

Manufacturing biologics – whether originator products or biosimilars – requires a high level of expertise, which may be in short supply at the start of a country's journey to bio-manufacturing.

The path for LMICs to begin production of monoclonal antibodies is very often through making biosimilars. Opting to produce biosimilars save costs and the many years of research required for developing a new antibody treatment. It makes it possible for companies to pick an already well-known, proven product with a history of success before innovating in designing novel antibodies.

Manufacturing biologics – whether originator products or biosimilars – requires a high level of expertise, which may be in short supply at the start of a country's journey to bio-manufacturing. Working with living organisms introduces variability, and even a small change to the manufacturing or testing processes can affect the quality and efficacy of the products. As biologics are commonly administered in the form of injections, their manufacture and testing are subject to the most stringent quality standards, which can be challenging and costly for new producers to meet. The good news is that, in increasing numbers, producers in LMICs are successfully overcoming all these challenges to produce biologics for the domestic market and, in some cases, for export.

The biomanufacturing process typically involves several steps, ranging from incorporating raw materials to drug substance manufacturing, all the way through to final drug product filling and packaging. Drug substance manufacturing typically is broken into upstream, downstream, and formulation. As explained below in more detail, the closer one moves towards formulation, the higher the value of the drug substance.

Figure 3. WHAT ARE BIOLOGICS?

	Vaccine	Recombinant Proteins & Plasma Derived Proteins	Monoclonal Antibodies	Cell & Gene Therapy
Indications	Infectious diseases prevention	Protein deficiency replacement	Oncology Auto-immune diseases	Oncology (CAR-T) Gene replacement
Cost of Manufacturing	Low-high	Low-medium	Medium-high	High
Cost of Treatment Range	Low-medium	Low-medium	High	High
Manufacturing Complexity	++/+++	++/+++	++	+++
Templated Process	Yes/No	No	Yes	No

Source: Merck internal assessment

Upstream processing consists of cultivating an expression system (mammalian or insect cells, yeast, or bacteria) in a bioreactor or fermenter to generate the desired therapeutic, or, in the case of vaccines, the desired antigen. For some biological processes, this production stage may be absent, for instance, if the drug substance can be directly extracted from animal or human-derived material (for blood and plasma-derived products, growth or fertility hormones, etc.). Animal cell-derived processes – used to make monoclonal antibodies, certain vaccines, and gene therapy products – is usually more costly, due to the high value of the raw materials needed for cell growth and substance expression.

Downstream processing includes several purification steps, such as filtration, chromatography, and precipitation, to isolate the drug substance and meet safety and efficacy requirements.

Once purified, the drug substance is formulated in a solution to enhance its stability and efficacy, followed by a fill-and-finish step, during which the drug substance is put into vials, ampoules, or, and syringes. Some products, in particular vaccines, are freeze-dried at this stage, which can add additional cost and complexity for the manufacturer. Also, in some vaccines, an inactive ingredient, or "adjuvant", is added to help create a stronger immune response in the patient. The drug substance is then tested and checked for quality before released further in the supply chain.

There is asymmetry in terms of the complexity of the various steps of biologicals supply chain, particularly between drug substance manufacturing (also referred as bulk production) and drug substance formulation, filling, and packaging. Very often the strategy for new producers is to begin with the simpler, lower value-added steps later in the value chain. Over time, they aim to advance to the more complex processes. Often, producers looking to begin vaccine production will start with fill-and-finish, or packaging and distribution.

Ideally, a producer that starts with fill-and-finish will subsequently move backwards along the value chain towards higher value activities, including production of the bulk vaccine antigen. This process, known as "backwards integration", is best carried out in close collaboration with a technology partner, such as a multinational company. The right technology partner can help local producers to improve their technical capacity in order to successfully move up the value chain.

The technologies for plasma production are well-established, and their manufacture is technically feasible for local producers provided they have access to an adequate volume of blood donations. To be commercially viable, any plasma production needs to be on a large scale and requires the use of end-to-end production facilities. For this reason, countries with large populations are best positioned to produce plasma domestically. Examples of LMICs with plasma therapies manufacturing capabilities include Argentina, Cuba, Venezuela, Thailand, Iran, and South Africa.

Finally, cell and gene therapies, sometimes referred to as "novel modalities", are a promising class of products that are subject to evolving regulatory guidance. While most of the R&D and product approvals are located today in high-income countries (HICs), attention is starting to turn to LMICs. Novel modalities require complex manufacturing processes in which sometimes the product is the process itself, with limited purification steps taking place due to the nature of the substance; this is the case, for instance, for treatments with autologous patient cells. Manufacturing processes for these offerings are still evolving to meet scalability, cost effectiveness, and overall industrialization targets.

During the last 20 years, bio-manufacturing has evolved significantly in response to the growing need to produce cost-effective therapies and vaccines, and innovative technologies have been central to this evolution. The investments required to set up and operate manufacturing facilities have fallen dramatically. Facilities can now be set up much more quickly and flexibly than in the past, to operate more efficiently while maintaining the ability to react to changes in the marketplace.

The application of new technology solutions, provided by knowledge partners such as Merck Life Science, is transforming biologics manufacturing. As these technologies develop, the cost barriers to entry decline.

Single-use and continuous processing systems are notable examples. Biologics such as monoclonal antibodies can now be made in one continuous system rather than having to move them from machine to machine during each stage of the production process. Continuous processing enhances quality, safety, and efficiency. Single-use systems improve safety by making it easier

Figure 4. MANUFACTURING STRATEGIES

for facilities to appropriately disinfect equipment between each use, and to switch production between molecules. This approach involves manufacturing using custom-made, high-quality plastic bags rather than stainless steel tanks.

"Bioprocessing 4.0" approaches – the cutting-edge of bio-manufacturing – build on the benefits provided by continuous processing. These combine advanced process technologies with software, automation, and analytics into one system that gives manufacturers a view of the entire manufacturing process, as opposed to individual units within the process. Adding connectivity helps to increase speed and lower costs.

Other solutions that generate efficiency gains in bio-manufacturing, while meeting with stringent regulatory requirements, include new testing systems that can slash the time required to test batches of medicines by as much as 80%, thus expediting the availability of new life-saving treatments for patients. Modern testing systems can enhance productivity by enabling manufacturers to acquire, aggregate and analyze data from disparate sources such as equipment, batch records, databases, and historians across the bioprocess.

Figure 5. BIOLOGICS MANUFACTURING PROCESS

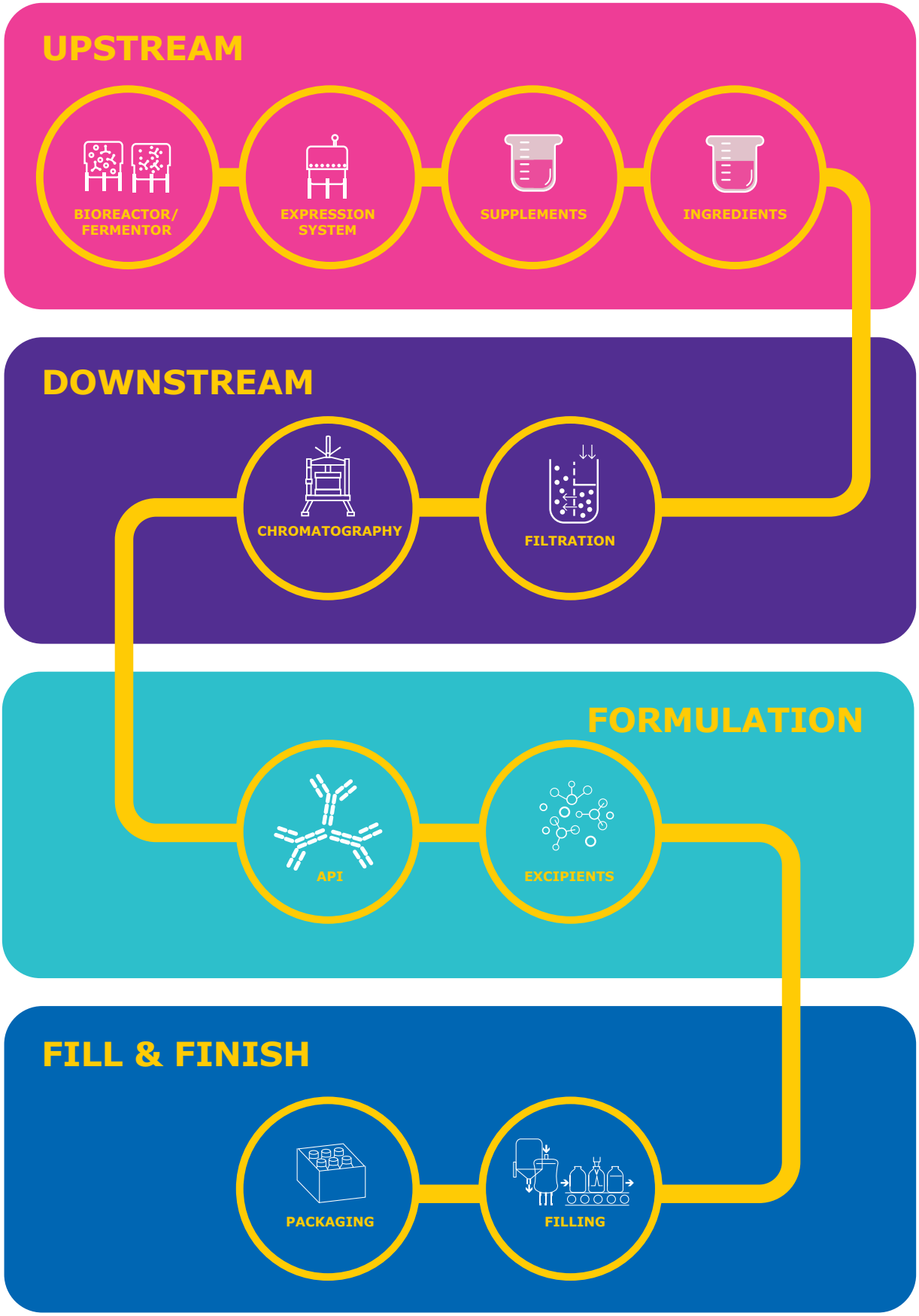
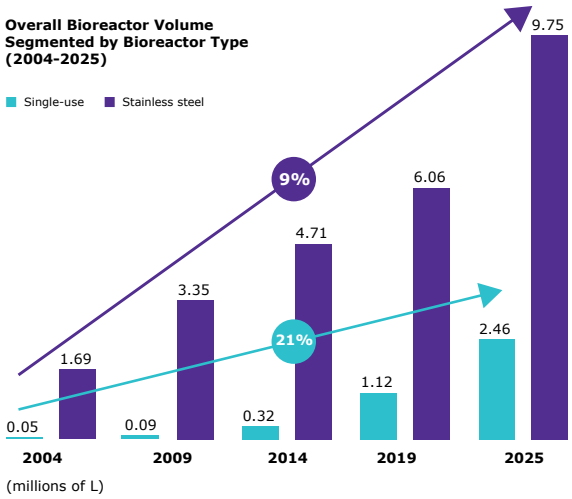


Figure 6. EVOLVING TOWARD SINGLE-USE TECHNOLOGIES

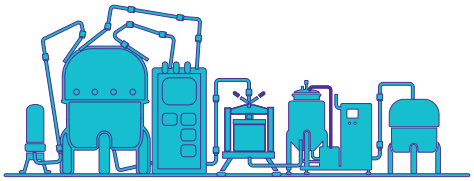


Sources: bioTRAK bioreactor data; Merck internal assessment

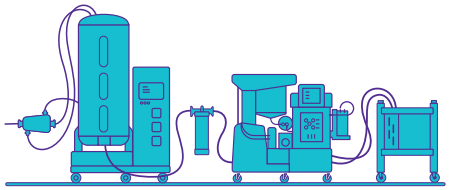
For all types of biologics, ramping up manufacturing capacity requires the right types of government action as well as technology partnerships, often with multinationals. Government support for the establishment of biologics R&D and manufacturing capacity includes direct investment in the sector, support for training and capacity building, and updating regulatory frameworks. Advance purchase agreements, in which the government pledges a percentage of its vaccine-procurement budget for local purchase, is another policy approach that shows promise.

Figure 7. ADVANTAGES OF A MANUFACTURING FACILITY EQUIPPED WITH SINGLE-USE TECHNOLOGIES VERSUS TRADITIONAL VACCINE MANUFACTURING PLANTS

Traditional large biological manufacturing facilities



Manufacturing facility using single-use technologies



	Traditional Stainless Facility	Single-use Facility
Capex required	~$500M to $1B	$20-100M
Time to construct	5-10 years	1.5 years
Change over time	4 weeks	0.5 days
Footprint	~>70,000 m²	~11,000 m²

Source: Flexible Manufacturing of Vaccines[2]

4. Investing in Domestic and Regional Capacity

At the global level, extending manufacturing networks can improve future pandemic preparedness. At the national level, local production can help to save money while setting the stage for regional and/or global exports.

Bio-manufacturing can have a positive effect on manufacturing proficiency and scientific skills, which in turn can spur industrial growth and boost competitiveness across sectors. Investments in establishing or stepping up production can, over time, enable local producers to produce larger volumes, scale up production in times of need, and, ultimately, contest markets abroad. Moreover, reducing expenditure on importing costly treatments can empower healthcare systems to invest funds in local services, including measures to improve pandemic preparedness.

But where should countries begin? After all, the development of a bio-manufacturing sector requires not just funding, but also specialized knowledge, skills, equipment, and access to intellectual property (IP). How to obtain these may not be immediately obvious.

Countries have relied on a range of pathways to success. These differ in approach, depending on country-specific factors, but their objectives are the same: bring affordable biologics to market, ensure quality and safety in production, and boost the competitiveness of local producers over time. Post-COVID, countries are setting an additional goal: enhance pandemic preparedness. The COVID-19 pandemic showed that investments in bio-infrastructure can create an important foundation for responding to health crises.

An element common to all the pathways is a sound regulatory system. Part of creating the foundation for developing a thriving biosimilars industry is putting in place regulatory pathways for biosimilars approval.

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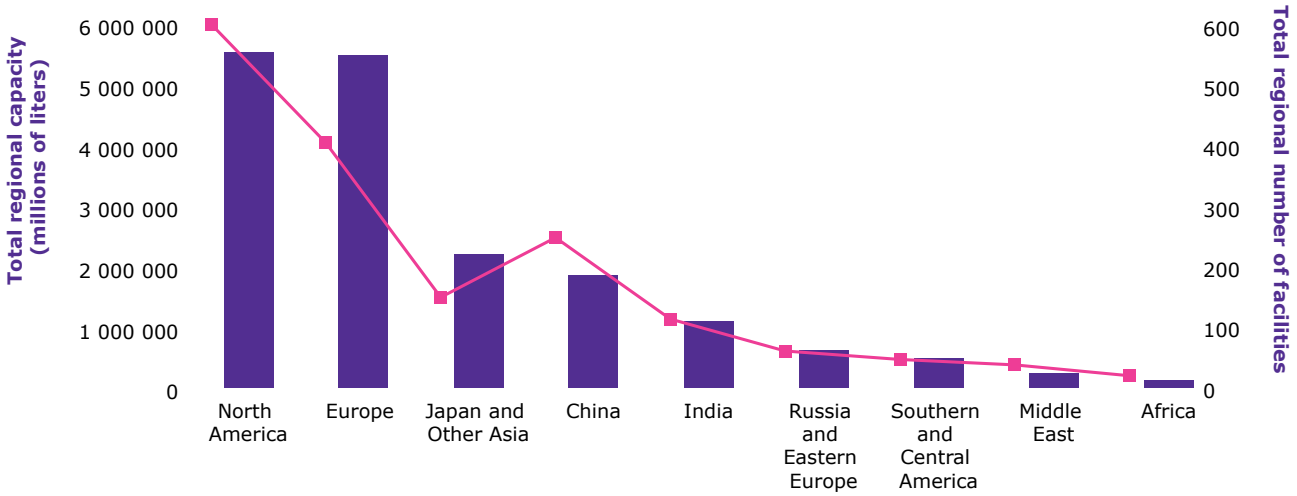
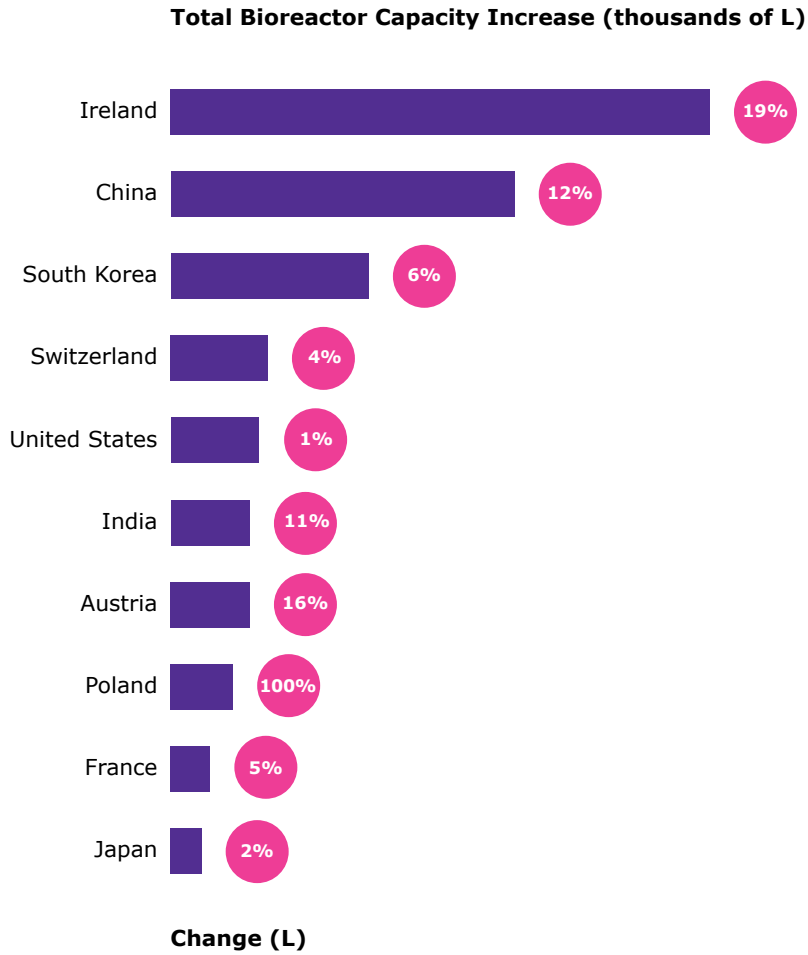
Figure 8. GLOBAL BIOMANUFACTURING CAPACITY BY REGION



Sources: BioPlan 2021; Langer and Rader 2021

Figure 9. PROJECTIONS FOR GROWTH IN BIOREACTOR CAPACITY 2019 - 2025: TOP 10 COUNTRIES



Growth in capacity projected for the period 2019 - 2025
The top 10 countries account for 91% of total capacity.
Sources: bioTRAK bioreactor data; Merck internal assessment

public safety must be the main benchmark. This is especially true for biologics, which are injected. The bar for safety and efficacy can and should be held ever higher, consistent with the most stringent standards globally. Efforts to harmonize regulatory standards – for example, through the Pan American Health Organization (PAHO) – are making progress, and more countries are now matching the standards of the World Health Organization (WHO).

Another common element is partnership. Partnerships with established, often foreign, technology providers are crucial to enabling local manufacturers to enter the value chain and accelerate domestic and regional vaccine production. Multinationals, in particular, have substantial internal expertise in relation to scale, innovation, and resources.

Pathway to biologics production: State-supported strategic shift

Governments play an important part in enabling biologics production, and their role is essential in one strategy in particular: that of a state-supported shift to increase biologics production. In this pathway, the government takes the lead in the process by making a strategic decision to rapidly build local players' capacity to produce biologics. The goal is to establish the entire value chain within the country under the umbrella of one grand initiative.

This has been the strategy, for example, in Brazil, where the government decided to invest in biologics production as an alternative to importing costly medicines. At one point, the country's universal healthcare system was spending a

reported 30% of its budget on imported biologics treatments. The Brazilian government's approach was to establish Public-Private Partnerships ("PPPs" in Portuguese), and to do so on a large scale. Today, of the approximately 100 PPPs currently operational in Brazil, thirty are focused on biologics.

These PPPs are collaborations between Brazilian manufacturers and non-Brazilian biologics producers in which knowledge transfer is exchanged for secure and reliable market access. This benefits both parties. In a typical PPP, a local pharmaceutical firm applies to establish a facility, in collaboration with a non-Brazilian knowledge partner, to develop biopharmaceuticals, following a roster of priority healthcare treatments produced by the government. These partnerships can start small; for instance, the local partner may initially oversee only simple tasks such as the labelling of vials. But they are designed to steadily increase the capacity of local facilities over time, until they become fully functioning production centers.

In return, the knowledge partners – typically established, foreign biologics manufacturers – are ensured entry into the market. Indeed, Brazilian and foreign PPP partners, working together, can obtain as much as a guaranteed 50% market share in the public procurement of their target product. This is of crucial importance in a country where government purchases make up 90% of the healthcare sector.

Brazil's PPPs are unique, in that each collaboration between a Brazilian and a foreign firm is matched by a parallel, government-run facility. Throughout the life of each PPP, a third-party government facility receives the knowledge transfer given to the Brazilian PPP partner by the foreign partner and works to build expertise within Brazil. This provides a kind of insurance for the government; even if the normal (private) Brazilian PPP partner disbands, this buildup of knowledge allows the government to step in and ensure ongoing production.

Many years ago, South Korea employed a different, successful government-led strategy. The Government focused on matching the world's highest regulatory standards in order to attain global competitiveness. The South Korean government urged manufacturers and local regulators to match the stringent standards of the United States' FDA and Europe's EMA, using extensive tax breaks for local producers to keep down costs and help them comply. Meeting these high standards increased the global competitiveness of many South Korean manufacturers and allowed them to engage in contract manufacturing for global players in biologics production, including US-based companies.

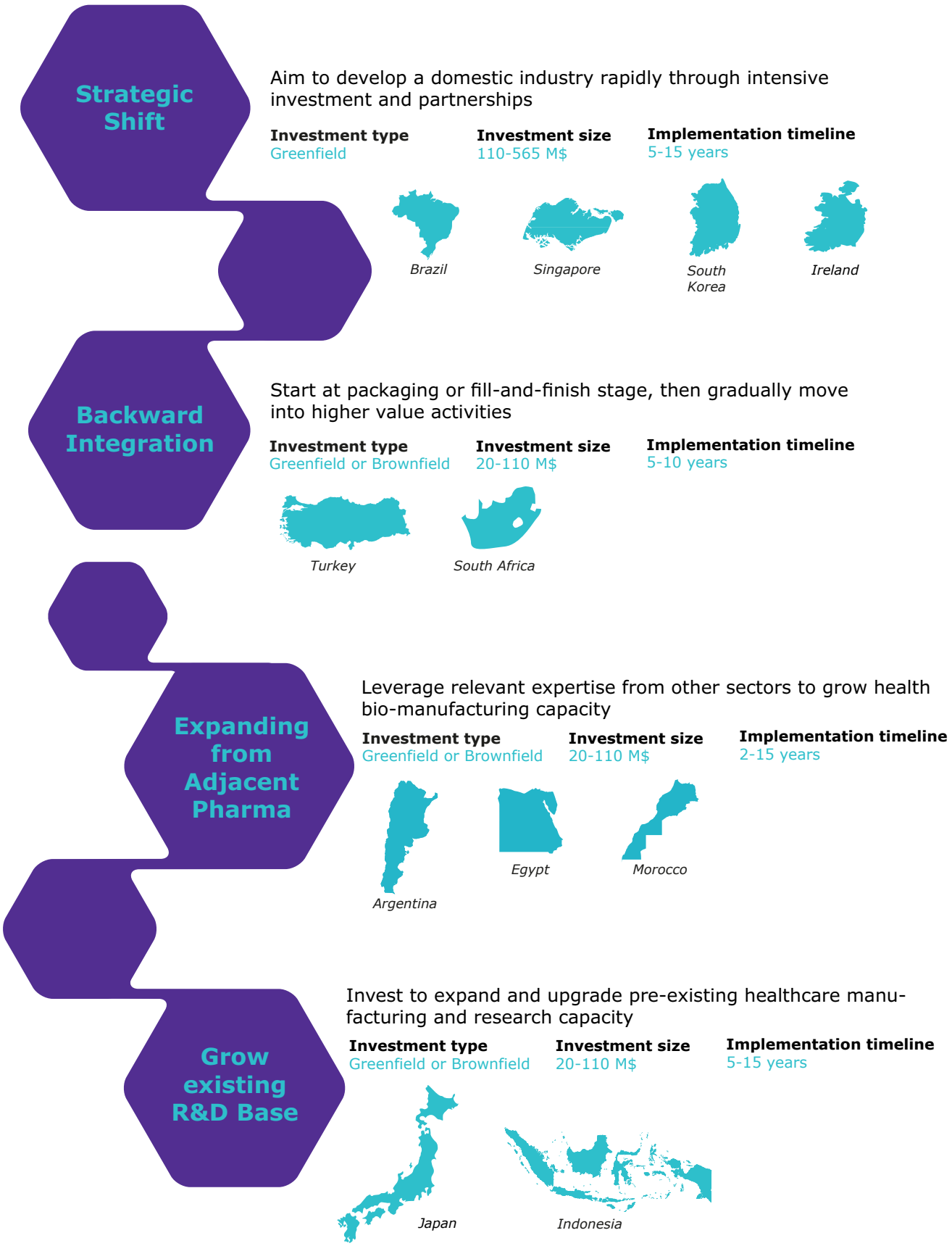
The strategy of proactively pursuing compliance with global market standards resulted in the rapid development of South Korea's bio-manufacturing industry. A decade ago, only a handful of small South Korean companies dabbled in pharmaceuticals. Today, the country is approaching global leadership in the manufacturing of biologics and biosimilars. Indeed, South Korean firms are now knowledge transfer partners for companies in countries that are developing their own bio-manufacturing sectors. In 2021, South Korea announced a new initiative to invest more than $20 billion, remove tariffs on bio-pharmaceutical inputs and equipment, and stimulate collaboration with producers from other nations notably the United States, in order to move its domestic biologics industry into the top 5 globally by 2025.

Pathway to biologics production: Invest in "backwards integration"

Another approach is to rely on "backwards integration" over time to develop vaccine and monoclonal antibody production capacity. This pathway involves the government supporting the establishment of facilities which begin with simple production processes and then move up the value chain over time. In the pathway described in the above section, the government undertakes a program to install all aspects of capacity and create a fully integrated domestic industry. This approach involves the government working to give local producers a foothold from which they can later grow their capacity.

Backwards integration is a common strategy employed by newer producers in order to get a foothold in the biologics market. It consists of companies beginning with the simpler, lower value parts of the production process then moving on to more advanced processes once they have established themselves. In the early stages, the established partners carry out the tasks in the other parts of the value chain. This pathway

Figure 10. PATHWAYS TO BIOLOGICS PRODUCTION



Greenfield investments relate to new production facilities; Brownfield investments involve upgrades to existing facilities.
Source: Revenue estimated based on Merck internal assessment. Country examples list not exhaustive.

usually entails local manufacturers beginning at the second step of the production process, fill-and-finish, then moving backwards along the value chain towards production of the core product.

The case of South Africa is an example of this approach, although success was not achieved overnight. It took the local company partnership Biovac five years of business to attract its first knowledge partner. After observing the difficulty of South African firms in attracting global partners, the government decided to speed up the process by providing incentives to draw in foreign firms with expertise that is integral to building local skills. The government also invested time, effort, and resources to provide training opportunities to build local expertise, including through on-the-job and even overseas training. In 2021, South African firms such as Biovac and Afrigen Biologics joined the WHO and other partners in establishing the first African mRNA manufacturing hub in Africa, for which they will carry out fill-and-finish for COVID-19 vaccines.

In Turkey, the government is taking a similar approach, focusing on investing in human capital and working to attract foreign direct investment (FDI). On the human capital side, the government has invested in both research and development programs and skills training. To stimulate FDI, the Turkish government has slashed tariffs on bio-manufacturing inputs. It has also ensured demand for sector-relevant firms through strategies such as offering purchase guarantees for manufacturers of products, such as insulin, that are willing to set up facilities in Turkey.

Though Turkey's strategy is still in its early stages, it is showing signs of success. For instance, a company producing monoclonal antibodies – launched in 2014 with substantial government R&D and production investments – recently began production, and several manufacturers are choosing to perform their fill-and-finish operations in Turkey.

Pathway to biologics production: Shift relevant expertise towards biologics

It can be daunting for fledgling producers to contemplate the complex processes and know-how required for bio-manufacturing. Countries with existing industries that employ similar skills to those required in biologics production may have an advantage, as they already possess at least some of the human capital necessary for the undertaking. A third pathway to building a domestic biologics industry, therefore, consists of redirecting relevant expertise from other sectors towards that of health bio-manufacturing.

Argentina is an example of this approach. As with other Latin American countries, it experienced a shift in its domestic health burden in recent years. The country has a relatively lower incidence of infectious diseases today, compared to ailments that typically have preoccupied the developed world, such as cancer, heart disease, and diabetes. The government recognized early on that boosting domestic capacity in biologics production could allow it to address this shift towards so-called non-communicable diseases (NCDs) while lowering public healthcare expenditure and creating export potential. At the same time, it faced a significant obstacle: a lack of funds to import needed expertise.

The agricultural genetic engineering industry and the health industry both benefitted from a broad base of genetic engineering professionals.

This unique approach allowed Argentina to create, over time, a significant biosimilars industry. The Argentinian manufacturer mAbxience, for example, has been running two successful biosimilar-manufacturing facilities for a decade, and has opened additional facilities in Spain. This global presence enables the firm to bring in technical experts from Europe to share expertise. Currently, there are half a dozen firms manufacturing biosimilars in Argentina. The results of the government's strategy have been significant, allowing the country to save a reported US$400 million in healthcare costs and to target export markets in Latin America and beyond.

Long before Argentina employed this strategy, Singapore did the same. This country took advantage of existing pharmaceutical expertise in the area of small molecules in order to shift towards biologics. Government programs were central to this approach. The Singaporean government worked to attract top scientific talent to the country's academic institutions. At the same time, tax deductions for qualifying R&D activities played a key role, and various grants for

skills programs resulted in the training of some 30,000 engineers and technicians in the last decade alone. The Singaporean strategy has been highly successful, resulting in Singapore's status today as a global manufacturing hub for biologics. BioNTech revealed in mid-2021 that it would site manufacturing operations in the country.

Pathway to biologics production: Expand on the existing knowledge base

A fourth pathway for expanding biologics production capacity takes a similar approach to that described in relation to Argentina and Singapore. However, rather than transferring expertise from another sector, this pathway builds on an existing R&D base in biologics. In countries that already have some degree of R&D base in the biologics sector, a simple, systematic expansion of that R&D, especially if it follows a strategic plan, can create the conditions for growth in bio-manufacturing and R&D capacity over time.

Indonesia is an example of this approach. There, an established, government-run institute for R&D was transformed, over time, into a successful biologics production operation. The initial R&D institute provided a foundation for the industry. The state-owned company Bio Farma had its first foray into vaccine manufacturing through a knowledge transfer partnership with Japan's Biken research institute to produce the polio vaccine. After this successful venture, the company expanded its operations by engaging in contract manufacturing partnerships with producers in India.

Bio Farma's growth was guided by a long-term strategy, based on a series of five-year plans. It includes consistent investments in education and training, in close cooperation with the government. For instance, government scholarships have enabled local talent to study overseas, and special incentive programs have allowed the country to bring home scholars who spent time abroad.

Today, Bio Farma is continuing to expand its capacity and scope of work. Confident in its vaccine-manufacturing ability, the company is now advancing into producing cancer-fighting monoclonal antibodies, at a moment in time when cancers are an increasing health concern in Indonesia.

5. The Role of Knowledge Partners

The pathways above represent different approaches by which LMICs can grow their domestic biologics industries. But countries are seldom able to implement these blueprints using only their own knowledge and resources. There is another element, in addition to government support, that is crucial for bio-manufacturing success: knowledge partners.

Partnerships for knowledge transfer come in many different forms. Knowledge and technology partners can be, for example, research institutions or companies. Partnerships can also exist between different players in developing countries, as well as between those in developing and developed nations. Experienced knowledge and tech transfer partners can help local companies to design production facilities, outsource some aspects of production to other firms, or, indeed, procure equipment and the knowledge of how best to use it. The duration of such partnerships can vary. This can depend on factors such as the number of expatriate staff at the local company and the presence (or absence) and quality of domestic academic institutions.

Knowledge partners can be either for-profit companies – for instance large multinationals with manufacturing capacity and know-how that can benefit new producers – or non-profit institutions, such as international organizations and government-funded research institutions. What they all have in common is the possession of an asset that they can share with local producers to help them increase capacity and move up the

Partnerships for knowledge transfer come in many different forms. They help local producers to move up the value chain.

value chain. These assets include but are not limited to intellectual property, know-how, and industrial capacity.

Knowledge partnerships come in many forms, and partners can generally benefit local producers by:

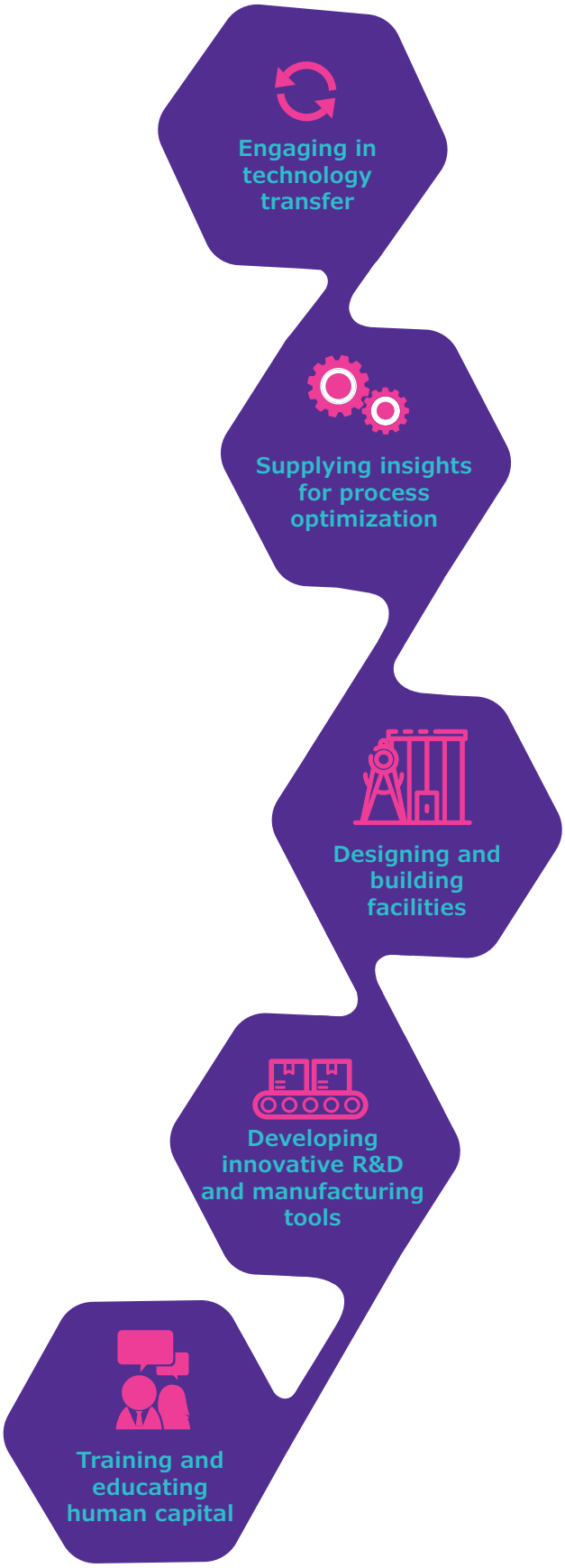
- Engaging in technology transfer;
- Supplying insights for process optimization;
- Designing and building facilities;
- Training and educating human capital; and
- Developing and supplying innovative R&D and manufacturing tools and technologies.

Partnerships that involve knowledge transfer benefit both the technology provider and local partner. Working with a local company simplifies market penetration for the multinational and can help it to navigate complex regulatory environments, by building on existing relationships with government bodies and customers, and to reduce manufacturing costs. Local companies, meanwhile, gain expertise and insights that enhance efficiency and make it possible to scale production and move up the value chain.

There are many examples of successful technology transfer, including the above mentioned state-led public-private-partnership program for biologics production in Brazil, which has brought in technology and expertise from foreign producers in exchange for market share on the Brazilian market.

Partnership with a major global manufacturer can be an effective way to accelerate the process of enter the market. An example is the Egyptian government's partnership with Grifols, one of the world's leading producers of plasma-derived medicines, to build domestic production capacity. This mutually beneficial partnership, formed in 2020, allows Egypt to reach higher levels of self-sufficiency in the production and procurement of plasma-derived therapies, and for Grifols to bolster its presence in the Middle East and Africa.

Figure 11. KNOWLEDGE PARTNERSHIP



Merck Life Science has partnered with research institutes and companies to accelerate bio-manufacturing capacity building. For instance, the company worked with Oxford University's Jenner Institute to develop a robust, cost-effective, and scalable vaccine manufacturing platform to accelerate vaccine development and manufacturing. Notably, this project provided the foundation for a Covid-19 vaccine-manufacturing process, which was transferred to manufacturing partners worldwide. Similarly, Merck's partnership with Texas-based Baylor College of Medicine to optimize a schistosomiasis vaccine has helped develop platform for vaccine manufacturing, including the one used to produce the vaccine against COVID-19 transferred to Biological E in India. Merck is currently engaged in a number of manufacturing process development projects in LMICs, including Tunisia, Egypt, Nigeria, Indonesia, and Taiwan.

The Life Science division of Merck KGaA is partnering with several companies and institutes in the world to advance their bio-manufacturing capabilities through:

- Providing cutting-edge solutions for bio-manufacturing processing and testing;
- Supporting process development, by applying 20+ years of expertise and leveraging M Lab™ Collaboration Centers;
- Developing and producing clinical and commercial monoclonal antibodies and viral gene therapy products;
- Conducting quality control and assurance testing for various biologics offerings; and
- Providing engineering solutions to conduct facility design, set-up, and operation.

Leveraging its expertise and know-how from contract manufacturing of biologics, Merck has also supported several manufacturing set-up projects, including with biosimilars manufacturer Turgut in Turkey and with Indian CDMO firm Stelis Biopharma.

Productive partnerships can include collaborations not just between individual companies, but also among members of regional organizations focused on vaccine security. Non-governmental organizations such as the African Vaccines Manufacturing Initiative (AVMI) and the Developing Country Vaccines Manufacturers Network (DCVMN) provide support to established, as well as early-stage, manufacturers. Importantly, exchanges between these producers in developing countries are taking place. In South Africa, meanwhile, Biovac has developed a technology package for the manufacture of Hib conjugate vaccine, which has already been transferred to two partners abroad; one of these partners has already successfully commercialized a pentavalent vaccine using this technology, and the other has begun clinical trials.

These networks offer concrete benefits, such as guidance on how to access technology and know-how and, importantly, a sense of solidarity. The sharing of lessons learned and challenges overcome can help small producers to improve performance while reassuring them that they are not alone.

M Lab™ Collaboration Centers:

The M Lab™ Collaboration Centers are high-tech environments meant to foster creative and rigorous collaboration between various pharmaceutical and biopharmaceutical manufacturers. In these spaces, companies have the opportunity explore new ideas and techniques, and can work directly with Merck Life Science's scientific and engineering experts. Importantly, the Collaboration Centers give local scientists access to sizing and simulation tools and methodologies, analytical and modelling support, training sessions and educational programs. The result is a space in which manufacturers, academics, government advisors, regulators, and industry associations can learn how the industry can increase productivity and improve processes while mitigating risks. M Lab™ Collaboration Centers are recognized as important contributors to development of the scientific and technical talents in several countries.

6. Insights for Policymakers: Promoting Bio-manufacturing in the post-COVID World

Even before the outbreak of COVID-19, most developed and many developing countries adopted strategies for the promotion of the biopharma industry, primarily targeting the production of finished medicines. The emergence and global spread of the pandemic resulted in a massive increase in government attention to bio-manufacturing and, in particular, the vaccine supply chain.

As the world emerges from the COVID-19 crisis and governments shift their focus to preparedness and long-term supply chain security, there is a critical need for clarity on what policies countries should adopt, either individually or in concert, to both nurture and preserve scientific innovation and ensure supply resiliency in biopharma, an industry now recognized as critical to national security.

The successful pathways used by countries in the pre-COVID environment provide helpful references, but more important will be novel policies that address the new post-COVID paradigm. At the same time, there is a need to avoid a competitive race to the bottom where governments undercut one another with subsidies to create unsustainable local industries.

Below are several suggestions for a practical approach for governments to successfully cultivate a national biopharma manufacturing base. The first step should be clear definition of the national goals.

No single country can hope to create a completely self-sufficient and sustainable biopharma manufacturing value chain within its own borders. The production processes, components, and technologies are too varied and, most importantly, innovate too quickly for a backwards looking planning process to completely capture. An attempt to create an autarkic or closed system may result in significant wasted resources while failing to provide true security of supply.

A realistic and achievable goal could be the creation of a diverse talent pool that is able to innovate, adapt, and absorb new technologies, and a flexible manufacturing base capable of rapidly iterating tailored upstream components and producing downstream finished medicines. In essence, the ideal goal would be the creation of a vibrant, internationally competitive biopharma ecosystem.

Several practical policy measures can be undertaken by governments to achieve this goal:

- Establishment of dedicated training centers or programs for biopharma research, bioprocessing, and technical manufacturing personnel. The M Lab™ Collaboration network – with centers located in Brazil, France, the United States, India, China, South Korea, and Japan – is an example.

- Funding support for industry-led incubators, innovation centers, application labs and other facilities that bring upstream component and equipment providers together with downstream customers to facilitate the diffusion and adoption of new technology.

- Regulatory frameworks that encourage regulators to allow for pilots of innovative processes and support experimentation, including redeployment of existing capacity to new uses.

- Removal of all tariff and non-trade barriers to trade in biopharma and vaccine inputs, components and machinery. In particular, regulatory barriers to imports of new materials and components used in research and development should be removed to ensure local labs can access the latest technologies.

- Government financial support for the building of flexible, single-use biopharma manufacturing capacity sufficient to meet potential pandemic and essential medicine needs.

- Analysis of upstream manufacturing needs, including machinery and components, and adoption of a bespoke strategy of investments, public-private partnerships, or consortiums and stockpiling to ensure maximum flexibility and speed of response.

- Robust IP protection regimes combined with minimal restrictions on and active encouragement of technology transfer, licensing and technology sharing consortiums.

7. The Way Forward

Today, many countries are adopting new policies or adapting existing long-term strategies to the new, post-COVID significance of biopharma manufacturing. Examples include Korea's Global Vaccine Hub Strategy[3], Australia's Modern Manufacturing Strategy[4] and the continued growth of Singapore's ASTAR Bioprocessing Technology Institute[5].

Especially given the growing portfolio of technologies and insights available to fledgling producers, governments are well advised to focus on building local and regional bio-manufacturing infrastructure. Investments to do so are likely to deliver a host of benefits. These include: increased access to treatments, better healthcare delivery, improved scientific and industrial capacity and thus economic benefits, and more pandemic resilience. The time for prioritizing biologics production capacity is now.

Given the growing portfolio of technologies and insights available to fledgling producers, governments are well advised to focus on building local and regional bio-manufacturing infrastructure. Investments to do so are likely to deliver a host of benefits.

Figure 12. POLICY MEASURES

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